Remarks

Claims 1-8, 32, 41, 50, 51, 60-64, 73-81, and 90-91 are pending in the application. Claims 1, 41, 50, 60-62, 64, 73-81, and 90-91 have been amended to conform with the groups elected in response to the Restriction Requirement. Claims 9-31, 33-40, 42-49, 52-59, 65-72, and 82-89 were drawn to non-elected groups and, therefore, have been canceled without prejudice. Support for the claim amendments and cancellations can be found throughout the application, including the claims as originally filed. Therefore, no new matter has been added. Importantly, the claim amendments and cancellations should not be construed to be an acquiescence to any of the claim rejections. Rather, the amendments and cancellations are being made solely to claim more clearly the invention and to expedite the prosecution of the instant application. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 U.S.C. § 120. Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Election/Restriction

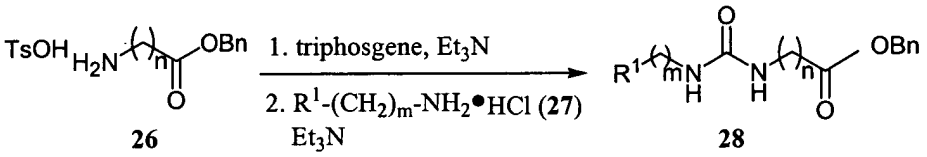
The Applicants gratefully acknowledge the rejoinder in part of Groups I and III. Accordingly, claims 1, 41, 50, 60-62, 64, 73-81, and 90-91 have been amended to conform to the rejoined Groups elected in response to the Restriction Requirement. Applicants request that withdrawal of method claims 41, 50, 60-62, 64, 73-81, and 90-91 be held in abeyance until allowable subject matter is indicated. Claims 9-31, 33-40, 42-49, 52-59, 65-72, and 82-89 were drawn to non-elected groups and have been canceled without prejudice.

Claim Rejections Based on 35 U.S.C. § 112¶1

Claims 1-8 and 32 stand rejected under 35 U.S.C. § 112¶1 as failing to comply with the enablement requirement. The Examiner contends that the instant Specification does not reasonably provide enablement commensurate in scope with the claims. Specifically, the Examiner asserts that the Applicants provide "very little direction in the instant specification," and "no working examples nor any in vitro or in vivo data." The Examiner further contends that pharmaceutical art "is unpredictable, requiring each embodiment to be individually assessed for physiological activity." The Applicants respectfully disagree.

The Applicants direct the Examiner to synthetic Scheme 1 (page 31 of the instant Application; reproduced in pertinent part below), wherein the Applicants provide a straightforward synthetic approach to the desired urea compounds of the invention via reaction (in step 2) of a primary amine with an electrophilic isocyanate intermediate (formed in step 1).

Scheme 1



26 **28**

The Applicants submit that the general transformations of the synthetic approach depicted in Scheme 1 are well known in the art. *See* Jerry March, Advanced Organic Chemistry-Reactions, Mechanisms, and Structure Fourth Edition, p 903, Reaction 6-17 (Wiley 1992). Therefore, the Applicants assert that one skilled in the art would realize that a variety of amine-containing compounds, and certainly primary amine-substituted heterocyclic or cycloalkyl compounds, would be acceptable nucleophiles in this scheme. Given the high level of knowledge of one of ordinary skill regarding the addition of amines to isocyanates, and the relative ease with which a chemist of ordinary skill may assess the effectiveness of a particular amine-containing substituent in the above-depicted transformation, the Applicants respectfully contend that no undue experimentation would be required to make and use the claimed invention. In further support of this position, the Applicants respectfully remind the Examiner that "Enablement is not precluded by the necessity for some experimentation such as routine screening ... [t]he key word is 'undue,' not 'experimentation.'" *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Moreover, contrary to the Examiner's assertion, the instant application provides numerous working examples as well as *in vitro* data correlating structure with HDAC inhibitory activity. *See generally Specification*, pages 70-85, including Tables 3 and 4. Given that inhibition is demonstrated for a variety of substitution patterns on the distal portion of the molecule, the data in Tables 3 and 4 effectively demonstrate the activity of the scaffold *as a whole*. As such, the Applicants assert that one skilled in the art would expect the claimed genus may be used for the disclosed utility without undue experimentation. Furthermore, the Applicants submit that "requiring each embodiment to be individually assessed for physiological

activity" would be unduly burdensome because the Applicants have demonstrated that the *in vitro* activities of the disclosed working examples substantiate their stated utility. Finally, the Applicants respectfully remind the Examiner that representative examples are sufficient if "one skilled in the art ... would expect the claimed genus could be used in that manner without undue experimentation." MPEP § 2164.02.

Accordingly, the Applicants contend that the application as filed complies with the enablement requirement for the pending claims and they respectfully request the withdrawal of the claim rejections based on 35 U.S.C. § 112¶1.

Claim Rejections Based on 35 U.S.C. § 103(a)

Claims 1-8 and 32 stand rejected under 35 U.S.C. § 103(a) based on the Examiner's contention that they are rendered obvious by the teachings of Richon et al. ("Richon") and published PCT application WO 02/26696 to Watkins et al. ("Watkins"). Specifically, the Examiner contends that based upon the structures disclosed in the two references, one of ordinary skill in the art would be motivated to synthesize the compounds of the instant invention. The Applicants respectfully disagree.

The Applicants respectfully contend that, prior to the Applicants' invention, the rejected claims were nonobvious in light of the combination of the Richon and Watkins references because neither reference suggests the desirability of modifying its compounds to provide the compounds of the instant invention. *See In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Critically, the motivation to modify the prior art must flow from some teaching in the art that suggests the desirability to make the modification needed to arrive at the claimed invention.

While the Examiner contends that compound 7 of the Richon reference differs from that of the instant invention by "just one CH_2 linkage," the Applicants assert that this characterization is an oversimplification; in fact, the compounds differ with respect to the substitution pattern on the urea functionality. Richon teaches a single urea-substituted hydroxamic acid with a functional group directly attached to the urea. In contrast, the compounds of the instant invention encompass a hydroxamic acid substituted with an alkylated urea and functional group variations thereof. Nevertheless, the Examiner relies on to the teachings of Watkins asserting

that Watkins teaches "aryl and heteroaryl groups not directly linked," and that these teachings provide the required motivation. The Applicants strongly disagree.

The Applicants respectfully remind the Examiner that when determining the differences between the prior art and the claims, the question under 35 U.S.C. 103(a) is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). The Applicants respectfully contend that the chemical and pharmaceutical properties of amide functional groups (taught by Watkins) are distinct from the corresponding chemical and pharmaceutical properties of urea functional groups (taught by Richon), causing the former also to have distinct pharmacological profiles from the latter. Therefore, the Applicants respectfully contend that the totality of the differences between the two classes of compounds is sufficiently great that one of ordinary skill in the art would not have had a reasonable expectation of success in the development of HDAC inhibitors based on applying the teachings of Watkins to the compound of Richon. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Accordingly, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

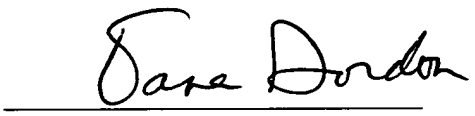
Fees

The Applicants believe they have provided for all required fees in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any additional required fee to our Deposit Account, **06-1448** reference **GUX-012.01**.

Conclusion

In view of the above remarks, the Applicants believe that the pending claims are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
Patent Group
Foley Hoag LLP

By: 
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